REMARKS

Applicants would first like to thank Examiner Frank Lu for his time and helpful suggestions during the telephonic interview on November 13, 2008 with Applicants' representative, Cheryl H. Agris and one of the inventors, Dr. James Donegan. The substance of the interview is provided below.

As discussed during the interview and as will be discussed in further detail below, the specification has been amended with respect to the Figure 18 legend.

Claims 91-123 are pending in the instant application. Claims 103, 105-109 and 120-121 have been canceled without prejudice. Applicants reserve the right to file continuation and/or divisional applications containing claims encompassing the canceled subject matter. Further as discussed during the interview, claims 91, 110 and 119 have been amended to more distinctly claim the subject matter of the invention. Specifically, the subject matter of canceled claim 105 has been incorporated into claims 91, 110 and 119. Furthermore, claim 119 has been amended to recite that the polymerase is RNA polymerase and thus incorporates the subject matter of claim 120. Thus, the amended claims contain no new matter and are supported by the specification.

I. SUBSTANCE OF INTERVIEW

A. Brief Description of any Exhibit Shown or any Demonstration Conducted

Applicants submitted Figure 18 of the specification since amendment to the Figure legend was discussed. Further, Applicants provided a copy of the Decision Granting Petition to accord application no. 09/302,817 the February 3, 1998 filing date.

B. Identification of Claims Discussed

Claims 91, 103, 105, 110 and 109 were discussed.

C. Identification of Specific Prior Art Discussed

As will be set forth in further detail below, Wagner et al. was discussed with respect to the rejections under 35 USC §102 and Wagner et al. and Henikoff et al. were

discussed with respect to the rejections under 35 USC §103. The double patenting rejection over US Patent No. 6, 986,985 was discussed as well.

D. Identification of Principal Proposed Amendments of a Substantive Nature Discussed

Amendments to claims 91, 110 and 119 were discussed.

E. Identification of General Thrust of Principal Arguments presented to the examiner

An enabling disclosure of the claimed subject matter has been provided. Further, the claims as amended are not anticipated or obvious over the cited references.

F. A General Indication of Any other Pertinent Matters Discussed

Applicants also discussed requirements for having the non-patent literature 2-14 from the Information Disclosure Statement made of record. The double patenting rejection was also discussed.

G. General Results or Outcome of the Interview

Applicants will provide copies of non-patent literature 2-14 in a Supplemental Information Disclosure Statement and in particular provide the publication date of the Promega catalog. Additionally, Applicants will amend the specification in response to the objection to the specification. Applicants agreed to submit arguments to support assertions of enablement. Furthermore, Applicants will set forth arguments as to why amended claims 91, 110 and 119 and other pending dependent claims are not anticipated and/or obvious over the cited references. Applicants additionally will address the obviousness double-patenting rejection.

II. Information Disclosure Statement

The Office Action specifically states

> Non-patent literatures 2-14 from the information disclosure statement filed on March 13, 2008 have been considered. However, since there are no publication dates for these non-patent literatures, these non-patent literatures cannot be put

> in the cover page of the patent if this instant application is issued. Therefore, these non-patent literatures in the 1449 form filed on March 13, 2008 have been struck through.

In response and as discussed during the interview on November 13, 2008, Applicants will submit a Supplemental Information Disclosure Statement containing copies of References 2-14. Applicants will specifically provide the publication date of Reference 2 (the Promega catalog). Further, Applicants note that references 3-14 are Office Actions issued in related applications. The dates noted on the Information Disclosure Statement are the dates these Office Actions were issued. Thus, pertinent dates have been provided with respect to references 3-14.

III. Specification

The disclosure is objected to on two grounds. Specifically the Office Action states:

> (1) although the amendments related to the specification filed on April 19, 2007 described that case *09/302,817* was filed on February 3, 1998, since the data from US Patent Office showed that case *09/302,817* was filed on April 16, 1999, applicant is required to provide data to support that case *09/302,817* was filed on February 3, 1998; and
>
> (2) although BRIEF DESCRIPTION OF THE DRAWINGS of the specification related to Figure 18 filed on April 19, 2007 describes IBI 31plasmid (plbl 31-BH5-2) (SEQ ID NOS:22-24) and BlueScript II plasmid construct (pBSIIIIHCY) (SEQ ID NOS:25-27), since plbl 31-BH5-2 contains three different nucleotides while plbl 31 pBSIIIIHCY contains three different nucleotides, it is unclear which nucleotide sequences in IBI 31 plasmid (plbl 31-BH5-2) and BlueScript II plasmid construct (pBSIIIIHCY) correspond to which sequences from SEQ ID NOS:22-27.

In response to the first assertion, as discussed during the interview with the Examiner on November 13, 2008, Applicants submit as Exhibit 1 a copy of the Decision granting the "Petition to Obtain a Filing receipt and Application Serial Number under 37 CFR 1.53", filed April 16, 1999, requesting that application serial no. 09/302,817 be accorded a filing date f February 3, 1998 as a divisional application under 37 CFR 1.53(b) based on prior application no. 08/182,621.

In response to the second assertion, as also discussed during the interview with the Examiner on November 13, 2008, Applicants have amended the legend to Figure 18

to more distinctly point out the corresponding Seq ID Nos. to the sequences set forth on Figure 18. No new matter has been added since the sequences set forth in the specification amendment are disclosed in the Sequence Listing.

In view of the above arguments, the submission of Exhibit 1 and the amendments of the specification, Applicants assert that the objections to the specification have been overcome. Therefore, Applicants respectfully request that the objections be withdrawn.

III. Enablement Rejection

Claims 91-105, 107, 108, and 110-123 has been rejected under 35 U.S.C. 112, first paragraph. It is asserted that

> the specification, while being enabling for making a protein-nucleic acid complex, does not reasonably provide enablement for producing a specific nucleic acid in a cell *in vivo* when any kind of conjugate recited in claims 91-105,107,108, and 110-123 is introduced into any kind of cell *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is thus concluded in the Office Action that

> The specification provides one with no guidance that leads one to claimed methods. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of any working examples related to the invention and the no teaching in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Applicants traverse the rejection for a number of reasons. First, it is asserted in the Office Action that

> Claims 91-105, 107, and 108 encompass any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one segment of said specific nucleic acid comprising a sequence coding for a protein and any kind of RNA polymerase wherein, when

> said conjugate is introduced into a cell *in vivo*, the conjugate can produce a specific nucleic acid. Claims 110-118 encompass any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one segment of said specific nucleic acid comprising a template for transcription, and any kind of RNA polymerase wherein, when said conjugate is introduced into a cell *in vivo*, said conjugate produces a specific nucleic acid. Claims 119-123 encompass any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one single-stranded segment comprising a sequence complementary to a primer present in said cell and any kind of polymerase wherein, when said conjugate is introduced into a cell *in vivo*, the conjugate can produce a specific nucleic acid.

In response to this assertion, Applicants note that in order to advance prosecution, claims 91, 110 and 119 have been amended to recite that the RNA polymerase (iii) is covalently linked to the nucleic acid of said protein-nucleic acid construct. Further claim 119 has been amended to recite that the polymerase is an RNA polymerase.

Applicants assert that these claims are certainly enabled by the specification. First, although T7 polymerase is a polymerase that does not require other auxiliary proteins, it was pointed out in the Office Action that some other RNA polymerases do require these factors. However, this point is moot as long as the conjugate is introduced into a cell that has these factors present. Secondly, Applicants note support is found in Figure 3(A-C) in the instant application which is entitled "Three Constructs with an RNA Polymerase Covalently attached to a Transcribing Cassette" clearly showing a conjugate made by covalently attaching an RNA polymerase to a series of three different nucleic acid constructs. Further, it is stated on the paragraph bridging pages 38 and 39:

> "The appropriate piece of DNA can be isolated and covalently attached to the RNA polymerase under conditions whereby the RNA polymerase after being covalently attached to a solid matrix (Cook, P.R. and Grove, F. Nuc. Acids Res. 20; 3591-3598 (1992)). Methods of modifying the ends of the

DNA molecules for attachment of chemicals are well-known (see for example, U.S. patent application Ser. No. 08/032,769, supra)."

A copy of Cook et al. is attached hereto as Exhibit 2. It should be pointed out that the Cook reference describes the modification of a T7 RNA polymerase by covalent attachment of a linker arm where the polymerase activity was still retained activity after this conjugation. Clearly, using the linker arm to attach a nucleic acid instead of the "immobilizing domain" used in Cook would be a harmless substitution that would still allow a conjugate to be formed that comprises an active enzyme. With reference to conjugation of this type it should also be mentioned that this is a commonly used technique that has been successfully employed with a myriad of different proteins and would not be considered to incur undue experimentation. As such it should be applicable to other polymerases besides T7 RNA polymerase.

Second, the Office Action asserts

> The specification provides working examples (see pages 43-63) for amplification of different DNAs and amplification from RNA template. The specification provides no working example for any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one segment of said specific nucleic acid comprising a sequence coding for a protein and any kind of RNA polymerase wherein, when said conjugate is introduced into a cell *in vivo,* the conjugate can produce a specific nucleic acid as recited in claims 91-105, 107, and 108, any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one segment of said specific nucleic acid comprising a template for transcription, and any kind of RNA polymerase wherein, when said conjugate is introduced into a cell *in vivo,* produces a specific nucleic acid as recited in claims 110-118, and any kind of conjugate comprising a protein-nucleic acid construct that comprises at least one promoter, at least one single-stranded segment comprising a sequence complementary to a primer present in said cell and any kind of polymerase wherein, when said conjugate is introduced into a cell *in vivo,* the conjugate can produce a specific nucleic acid as recited in claims 119-123.

Applicants disagree with the assertions made. It is Applicants position with regard to delivery of a nucleic acid-protein conjugate to a cell, methods were known at

the time for carrying out such a process. Wagner et al., US Patent No. 5,591,601, describes the use of "Lipofectin", a commercially available regent that can provides such means. This reagent was utilized later in a paper published by this group (Chen et al, 1994, Nucl. Acids Res. 22:2114-2120, which was attached to the Office Action) for delivery of a T7 RNA Polymerase/nucleic acid complex that was cited by the Examiner in the instant Office Action. A paper by Gao and Huang (1993 Nuc Acids Res 21; 2867-2872), attached hereto as Exhibit 3 also describe transfection of T7 RNA polymerase/nucleic acid constructs using a slightly different reagent: DC-chol cationic liposomes. To further support this assertion, Applicants herewith submit as Exhibits 4-5 the following references describing *in vivo* administration of DNA even before the priority date of the above-referenced application, January 13, 1994:

1. Gao et al, 1993, "Direct *In Vivo* Gene Transfer to Airway Epithelium Employing Adenovirus-Polylysine-DNA Complexes", Human Gene Therapy 4:17-24;
2. Wu et al., 1988,"Receptor-mediated Gene Delivery and Expression in Vivo", J. Biol. Chem. 263:14621-14624.

As such, it can be seen that the transfection of nucleic acids, proteins and protein/nucleic acid complexes was a standard method in the art at the time of the filing. There should be no technical barriers to transfection with a protein/nucleic acid conjugate compared to the protein/nucleic acid complexes described above.

Applicants further note that the pending claims are directed to protein-nucleic acid conjugates **not** to methods of use. Further, the preamble to the pending claims states "the conjugate, which when introduced into a cell..". Thus, the claimed conjugates could be expressed in cells ex vivo and in vivo. Even assuming *arguendo* that the claimed conjugates could not be used in vivo, the claims are directed to the product itself not the method. The Examiner actually concedes that the claimed conjugates are enabling for "in vitro" (ex vivo) use.

In view of the amendments of claims 91, 110 and 119 and the above arguments, Applicants assert that the rejections under 35 USC 112, first paragraph have been overcome. Therefore, Applicants respectfully request that the rejection under 35 USC 112, first paragraph be withdrawn.

IV. The Rejection Under 35 USC 102

Claims 91-93, 96-98,101,102, and 110-115 are rejected under 35 U.S.C. 102(e) as being anticipated by Wagner *et at.*, US Patent No. 5,591,601. It is asserted that Wagner *et at.*, teach all limitations recited in claims 91-93, 96-98, 101, 102, and 110-115.

Applicants respectfully traverse the rejection. Although Wagner reference does describe a complex where T7 may be bound to its cognate promoter on a nucleic acid this would not be considered to be a conjugate. The immediate effect of the Wagner construct would be the release of the polymerase its promoter and its progression down the template strand while making copies of RNA. As such, with reference to page 12 of the Office Action, Applicants do not believe that "Wagner et al., teach a conjugate". A person skilled in the art would not consider their examples to be conjugates *per se* but rather they exemplify complexes. The complexes described by Wagner are tenuous in nature and do not exhibit the stability that is commonly associated with compositions termed "conjugates".

However, in order to advance prosecution, claims 91 and 110 have been amended to recite that the RNA polymerase (iii) is covalently linked to said protein-nucleic acid construct (subject matter of claim 105). There is certainly no disclosure or suggestion of RNA polymerase covalently linked to the protein-nucleic acid construct.

Claims 92-93, 96-98,101 and102 depend from claim 91. Claims 111-115 depend from claim 110. Thus arguments made with respect to claims 91 and 110 would apply to the dependent claims as well.

In view of the above arguments and amendments, Applicants assert that the rejection under 35 USC 102(e) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

V. Rejection Under 35 USC §103

Claims 94, 119, 120, 122, and 123 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wagner *et at.*, as applied to claims 91-93, 96-98, 101, 102, and 110-115 above, and further in view of Henikoff *et at.*, (US Patent No. 4,843,003, published on June 27,1989). The Office Action specifically states:

> Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a conjugate comprising a single stranded nucleic acid construct as recited in claim 94 and a conjugate comprising a single stranded nucleic acid construct that comprises at least one promoter and at least one single-stranded segment comprising a sequence complementary to a primer present in said cell as recited in claim 119 using a single stranded cloning vector as a cloning vector in view of the prior art of Wagner *et al.*, and Henikoff *et al.*. One having ordinary skill in the art would have been motivated to do so because the simple substitution of one kind of cloning vector (i.e., the cloning vector taught by Wagner *et al,)* from another kind of cloning vector (i.e., the cloning vector taught by Henikoff *et al.,)* during the process of making a conjugate comprising a single stranded nucleic acid construct as recited in claim 94 and a conjugate comprising a single stranded nucleic acid construct that comprises at least one promoter and at least one single-stranded segment comprising a sequence complementary to a primer present in said cell as recited in claim 119, in the absence of convincing evidence to the contrary, would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the cloning vector taught by Wagner *et at.,* and the cloning vector taught by Henikoff *et at.,* are used for the same purpose (i.e., cloning nucleic acids) and are exchangeable (see Henikoff *et at.,* column 6, lines 50-62).

Applicants respectfully traverse the rejection. As noted above, Applicants assert that Wagner does not disclose conjugates. However, as also noted above, in order to advance prosecution, claims 91, 110 and 119 have been amended to recite that the RNA polymerase (iii) is covalently linked to said protein-nucleic acid construct (subject matter of claim 105). Thus, it would follow that claims 94, 122, and 123 would contain this limitation. Claim 120 has been canceled. Furthermore, in view of the amendment of claims 91 and 119, replacing the cloning vector of Wagner with the cloning vector taught by Henikoff et al. would not result in the claimed conjugate. Further, Applicants note that the secondary reference, Henikoff is directed to an unrelated process, a process for producing shorter circular DNA from larger target sequences. It is questionable as to whether there would be any motivation to combine the disclosures.

In view of the above arguments and amendments of claims 91 and 119, Applicants assert that the rejections under 35 USC 103 have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

VI. The Double Patenting Rejection

Claims 91-105, 107, 108, and 110-123 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of U.S. Patent No. 6,986,985. Applicants respectfully traverse the rejection. However, in order to advance prosecution, a Terminal Disclaimer is being submitted herewith.

SUMMARY AND CONCLUSIONS

It is Applicants belief that the pending claims are in condition for allowance. However, if a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

/Cheryl H Agris/

Dated: November 24, 2008

Cheryl H. Agris, Reg. No. 34,086
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EXHIBIT 1

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

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In re Application of :
Dean L. Engelhardt et al. :
Application No. 09/302,817 : DECISION GRANTING
Filed: February 3, 1998 : PETITION
Attorney Docket No. Enz-52(Div2) :

This is a decision on the paper styled "Petition to Obtain a Filing Receipt and Application Serial Number under 37 CFR 1.53" filed April 16, 1999, requesting that the above-identified application be accorded a filing date of February 3, 1998 as a divisional application under 37 CFR 1.53(b) based on prior application No. 08/182,621.

Petitioners allege that the original application papers were filed under former 37 CFR 1.60[1] in the Patent and Trademark Office (Office) on February 3, 1998, and subsequently misplaced in the Office. In support, the petition is accompanied by a copy of petitioners' postcard receipt acknowledging receipt in the Office on February 3, 1998 of a "Request for a Divisional Application under 37 CFR 1.60" and an "Application." A copy of the original application papers purportedly filed on February 3, 1998 was also supplied.

It is noted that petitioners' postcard receipt does not specify the number of pages of specification and drawings deposited on February 3, 1998. However, in view of petitioners' comments it is presumed that the "Application" indicated on the postcard is the specification and drawings for the above-identified divisional application. A statement included in the copy of the request for a divisional application, supplied with the present petition, verifies the accompanying divisional application papers as a true copy of prior application No. 08/182,621.

Pursuant to MPEP 201.06(a) "a continuation or divisional application filed under 37 CFR 1.60 on or after December 1, 1997, will automatically be treated as an application filed under 37 CFR 1.53(b)." Accordingly, petitioners' February 3, 1998 application filed under former 37 CFR 1.60 should be treated as though it were filed under 37 CFR 1.53(b).

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[1] 37 CFR 1.60 was deleted from title 37 of the Code of Federal Regulation effective December 1, 1997. See Notice of Final Rule, 62 Fed. Reg. 53132 (October 10, 1997).

The original 37 CFR 1.60 application papers cannot be located. However, in view of the evidence presented, the petition to accord the application a filing date of February 3, 1998 as a divisional application under 37 CFR 1.53(b), is granted. No petition fee is required.

It is noted that the original application papers filed on February 3, 1998 were accompanied by a petition to revive prior application No. 08/182,621. Because the petition to revive was granted in a Decision mailed April 15, 1998, the prior application was pending on February 3, 1998. Therefore, continuity between the above-identified divisional application and prior application No. 08/182,621 has been established.

Since the original application papers cannot be located in the Office, the duplicate papers received April 16, 1999, will be used for examination purposes. The application has been assigned application No. 09/302,817.

Applicant should notify this Office if the original papers are subsequently discovered in the Office so that the present duplicate file can be merged with the original papers and any duplicate filing fee refunded.

The application is being forwarded to the Office of Finance for charging the $395.00 filing fee to deposit account No. 05-1135, as authorized in the April 16, 1999 copy of the original request for a divisional application.

The application will then be forwarded to Initial Patent Examination Division for further processing as a divisional application under 37 CFR 1.53(b) based on prior application No. 08/182,621 with a filing date of February 3, 1998 using the application papers supplied on April 16, 1999. A filing receipt to that effect will be mailed in due course.

Thereafter, the application will be forwarded to Technology Center Art Unit 1634 for examination in due course.

Any inquiries related to this decision should be directed to James Engel at (703) 308-5106.

Fred Silverberg
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JJE